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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/334,537	06/16/1999	RAJA G. ACHARI	719-163	5432

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EXAMINER
WANG, SHENGJUN

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/24/2003

28

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/334,537	Applicant(s) ACHARI ET AL.	
	Examiner Shengjun Wang	Art Unit 1617	

-- The MAILING DATE f this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on May 19, 2003 has been entered.

Claim Rejections 35 U.S.C. § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. Claims 1-5, 7 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Hussain et al. (U.S. Patent 4,464,378, of record).

3. Hussain et al. teaches a nasal composition comprising analgesically effective amount of morphine wherein morphine may be in the form of acid addition salt. See, particularly, column 2, lines 45-62, and claims 16-17 and 34. Hussain particularly teaches an aqueous nasal composition comprising 15% of morphine sulfate with pH at about 4.5. See, example 2 in column 10.

4. Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by INFORMORPH (Physicians' Desk Reference).

INFORMORPH provides a pharmaceutical aqueous solution formulation of morphine sulfate at a concentration of 25 mg/mL at pH of 4.5. See, particularly, pages 985 the Description. As to the limitation "for intranasal administration," note, it is well settled that the "intended use" of a product or composition will not further limit claims drawn to a product or composition. See, e.g., In re Hack 114 USPQ 161.

5. Claims 1-4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Merkus, in view of the disclosure of The Merck Index (Eleventh addition, page 988-989).

6. Merkus teaches nasal composition comprising morphine sulfate and a carrier in the form of powder (see, examples 1A and 1B in column 8). Merck index discloses that morphine sulfate has pH of 4.5. Note the carrier employed in the nasal composition is neutral.

Claim Rejections 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 8-15 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merkus (US Patent 5,756,483 of record) in view of The Merck Index (Eleventh addition, page 988-989), or INFORMORPH (Physicians' Desk Reference).

9. Merkus teaches a known pharmaceutical aqueous solution formulation of morphine for nasal delivery comprising about 5% of morphine salt at pH of 6. The formulation also contains

applicant's preferred other pharmaceutical excipients, including a preservative, a phosphate buffer, a humectant, and an absorption enhancing agent. See, e.g., column 6, lines 37-50.

10. Merkus further teaches various morphine formulations for nasal delivery wherein the pH has not been expressly indicated. See, column 7, line 8 bridging column 8, lines 62, particularly, the examples. The formulations may also contain the thickening agent herein (methylcellulose) and humectant herein (sorbitol), See, particularly, the examples 1-3 in column 8. The morphine employed in examples 2-3 is a salt which include hydrochloride, sulfate and acetate. See, column 7, lines 12-15.

11. Merkus does not expressly teach a morphine formulation comprising all the ingredients herein (humectant, buffer, absorption enhancing agent, and thickening agent).

12. However, all the ingredients employed herein are known to be useful in morphine formulation for nasal delivery. The Merck Index teaches that the pH of aqueous solution of morphine sulfate and morphine hydrochloride is about 4.5 and 5 respectively. INFORMORPH reveals that morphine are known to be used in acidic pH clinically.

13. Therefore, the pH of the examples 1-3 in column 8 is reasonably believed to be about 4.5 to about 5, and it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to make a nasal morphine sulfate formulation containing all the ingredients herein (humectant, buffer, absorption enhancing agent, and thickening agent) at a acidic pH.

14. A person of ordinary skill in the art would have been motivated to make a nasal morphine sulfate formulation containing all the ingredients herein (humectant, buffer, absorption enhancing agent, and thickening agent), or with pH of 3.5 or 4 because it would have been

considered within the skill of the artisan to optimization a nasal formulation by using known excipient accordingly, such as adding methylcellulose (thickening agent) to make a gel formulation (example 2 in Merkus), or adding a proper buffer to adjust or stabilize the pH of the formula.

15. It is further noted that employing morphine sulfate or morphine chloride in examples 2 and 3 is obvious they are the two salts of the disclosed three salts therein. Employment of morphine sulfate and morphine hydrochloride would the pH of the formulation therein about 4.5 and 5 respectively, according the Merck Index.

16. Claims 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merkus (US Patent 5,756,483 of record) or Hussain et al. (of record).

17. Both Merkus et al and Hussain teach a pharmaceutical composition of morphine for nasal delivery with acidic pH as discussed in the prior office action.

18. The references do not teach expressly the particular pH herein.

However, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to formulate a similar composition with the pH herein.

A person of ordinary skill in the art would have been motivated to formulate a similar composition with the pH herein because the pH herein (3.5, 4.0) is close to the range disclosed to the rang expressly taught in the prior art. (4.5 and 6.0), and the prior arts do not particularly limit the pH range. The particular pH herein would have been reasonably view as an obvious

variation, or a matter of optimization according to a specific formulation, which is considered within the skill of artisan.

Response to the Arguments

Applicants' amendments and remarks submitted May 19, 2003 have been fully considered, but are not persuasive for reasons discussed below.

As to the teaching by Hussain et al., the examiner maintains his position stated in the office action mailed May 7, 2002 (paper No. 22). Specifically, it is stated : "Applicants' rebuttal arguments regarding Hussain reference asserted that a) Hussain's teaching in column 10, lines 45 to 50 should not be interpretated as a solution with pH of 4.5; b) Hussain's teaching of 15 mg/0.1 ml solution therein is inoperable, citing the experiment presented in Dr. Quay Declaration. These assertions again are found unpersuasive. Declaration of Dr. Quay has been carefully reconsidered. Applicant generated data, proffered to obviate prior art teachings, lacks the probative force accorded data generated by independent, disinterested parties. It is well settled patent law "that it is not a difficult matter to carry out a process in such a fashion that it will not be successful and, therefore, the failures of experimenters who have no interest in succeeding should not be accorded great weight" In re Michalek, 74 USPQ 108, at 109 citing Bullard Company et al v. Coe, 147 F.2d. 568, 64 USPQ 359. Regarding the solubility of morphine sulfate, applicants' attention is directed to Merck Index, page 989, the solubility of morphine sulfate may be very high, depending the temperature.

Regarding the pH, (paragraphs 6 and 7 in declaration), one of ordinary skill in the art would have not expect much, if any, pH change when a pH 4.5 solution with 90 (80 ml water, 15

gram nalbumphine and diluted sodium hydroxide) plus mL volume is diluted to 100 mL with water.

Applicants assert that Merkus reference is improper because the cited teaching is not the express teaching in Merkus patent, note the cited teaching shows the fact that at the time the claimed invention was made by applicants, the claimed invention has already been made by others. Whether, the teaching is the center issue of the patent is not relevant. Regarding the remarks of final pH of the cited formulation, applicants' attention is directed to the following facts, the total volume of the formulation is about 37 ml (30 ml buffer, 6 ml propylene glycol and 1.5 gram of morphine chloride). One of ordinary skill in the art would have not expected much deviation from the buffer pH since compounds with acidic properties (morphine hydrochloride) is in much small amount compared to the total volume. Further, any deviation would be toward acidic side, i.e. make the pH smaller since morphine hydrochloride is acidic. See, Merck Index, page 988."

Further, in view of Dr. quay's data presented in the declaration (paper No. 15), it is noted that a key parameter closely related to the solubility of a compound is not disclosed by Dr. Quay: the temperature at which the solubility tested. Furthermore, Hussain teaches a "composition" as the final product, not a strictly defined "solution." See column 10, lines 35-55.

Applicants' attack of operability of US patent is not a convincing arguments since every patent is presumed valid, and since that presumption including the presumption of operability (see MPEP 716.07).

As to the teachings by Merkus, note all the examples disclosed by Merkus is believed to have pH 4.5 to 5 according to the disclose of Merck index. Merkus's teaching provide evidence

that at the time of the claimed invention was made, nasal delivery of morphine at low pH is known in the art, contrary to Dr. Quay's statement made in the declaration. In view of the fact, it is concluded that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to employ a particular acidic pH in a nasal delivery morphine composition.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang, Ph.D. whose telephone number is (703) 308-4554. The examiner can normally be reached on Monday-Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Patent Examiner

SHENGJUN WANG
PATENT EXAMINER

Shengjun Wang

July 21, 2003